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The Synthesis of the C24-C32 Subunit of (+)-Ionomycin

by

Lisa Cameron

A thesis submitted in conformity with the requirements
for the Degree of Master of Science,
Graduate Department of Chemistry,
University of Toronto

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Abstract

The Synthesis of the C24-C32 Subunit of (+)-Ionomycin
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Described herein is the Lautens/Colucci total synthesis of (+) ionomycin, with specific attention being paid to the synthesis of the C24-C32 tetrahydrofuranyl subunit. To date, two previous total syntheses of (+) ionomycin, to be discussed, have been published by the groups of Evans and Hanessian. Also described is the general chemistry of the formation of tetrahydrofuran rings.

This tetrahydrofuranyl subunit, ring B of ionomycin, is derived from a geranyl acetate backbone. Sharpless asymmetric epoxidation and a diastereoselective epoxidation-cyclization sequence are the key manipulations applied to install the desired stereocentres. Each of the other three acyclic fragments of ionomycin arise from exploitation of the versatile chemistry of [3.2.1] oxabicycles. Chemistry developed in this laboratory which provides enantiospecific nucleophilic ring opening effects further skeletal elaboration.
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CHAPTER 1

INTRODUCTION TO THE CLASS OF
POLYETHER ANTIBIOTICS
AND
(+)–IONOMYCIN
1 Introduction

1.1 Introduction to Polyether Antibiotics

Monocarboxylic acid ionophores, also referred to as polyether antibiotics are a large group of natural products which act to chelate cations. These ionophores are comparable to crown ethers in their cation binding ability, but differ significantly in specificity. Crown ethers complex cations according to relative dimension of cation and macrocyclic cavity, while polyether antibiotics are able to chelate cations of varying sizes. This class of compounds, derived from various strains of streptomyces organisms, has stirred much interest in scientific circles. The interest stems from their unique ability to translocate inorganic cations through hydrophobic lipid bilayers, which results in a wide variety of biological functions. Some of these include antimicrobial agents, growth promoters in ruminants, and the initiation of cardiovascular responses in mammals.

Although the first polyether antibiotic was isolated in 1950, it was not until 1967 that a structural elucidation of a member of this class was achieved. The makeup of polyether antibiotics typically consists of a carboxylate group along with several additional oxygen ligands. Substituted tetrahydrofuran and tetrahydropyran rings, as well as spiroketal functions are prevalent in the architecture of these molecules.

The 70 polyether antibiotics that have been isolated to date present a formidable challenge to synthetic chemists. The differing stereochemical arrangement of functional groups has resulted in an unceasing flow of investigation and development of elegant methodology. Scheme I depicts a small selection from the class of polyether antibiotics.
1.2 Introduction to the Polyether Antibiotic (+)-Ionomycin

(+)-Ionomycin, (Scheme 2), was first isolated from the fermentation broths of *Streptomyces conglobatus*\(^{10}\) in 1978. Ionomycin is distinct from the other members of the polyether antibiotic family in several important ways. Firstly, it is doubly charged, and therefore highly selective for divalent ions. This property is in direct contrast to the monobasic chelating effects of other polyether antibiotics and allows ionomycin to chelate divalent ions as a dibasic acid in an octahedral coordination system, as a 1:1
charge-neutral complex.\textsuperscript{11} Calcimycin is the only other ionophore to similarly distinguish between monovalent and divalent cations, differentiating between calcium and magnesium as its 2:1 ligand/metal complex.\textsuperscript{12} A second anomaly is present in the β-dicarbonyl functionality at C\textsubscript{5}–C\textsubscript{11}, a rarity in natural products. This moiety accounts for two of the six charged ligation points,\textsuperscript{13} and the intense UV absorption band at 280 nm that is exhibited by ionomycin.\textsuperscript{14} Lastly, while the backbone of ionomycin consists of one long acyclic chain, and two furanoid rings, other ionophores of similar size are of a more polycyclic nature.\textsuperscript{15}

\textbf{Scheme 2}

The structure of (+)-ionomycin was elucidated in 1979 by Gougoutas et al.\textsuperscript{16} Structural determination was achieved by X-ray crystallography as well \textsuperscript{1}H and \textsuperscript{13}C NMR spectroscopic studies. The dianion salt of ionomycin exhibits an octahedral coordination to the central cation, typically, Ca\textsuperscript{2+}. 


5. H. G. Hanley and J. D. Slack, Ref. 4, Ch. 8; P. W. Reed and G. M. Bokock, Ref. 4, Ch. 9; M. W. Osborne, J. Wenger, M. Zanko, F. Kovzelo and M. R. Cohen, Ref. 4, Ch 10


CHAPTER 2

INTRODUCTION TO THE CHEMISTRY OF
(+) IONOMYCIN
2 The Chemistry of Ionomycin

2.1 Introduction

(+) - Ionomycin is constructed of a 32 carbon skeleton. Of these carbon centers, 14 exhibit asymmetry. Both a cis and a trans 2,2,5-substituted tetrahydrofuranyl ring system are present, as well as a trans disubstituted olefin, and three hydroxyl groups. A β-diketone and a carboxylic acid group complete the list of functionality. Also noteworthy are the alternating methyl groups from C1 to C16 and the propionate derived sequence that forms C17 to C22.
Constructing the ionomycin backbone with correct relative, and absolute stereochemistry, is a formidable challenge. A convergent synthetic approach readily simplifies this challenge. This strategy entails the construction of smaller, simpler pieces of the whole, which can then be joined with stereospecificity. Although the controlled combining of fragments is not always as straightforward as is hoped, and the final stages of any synthesis is a poor time to experience problems, convergency is still an excellent strategy.

Scheme II
Another advantage of a convergent synthesis is the ability to create functionality upon appending of subunits. Although risky, this approach is often desirable. In this way, the requisite functional groups do not necessarily need to exist within the individual fragments. The retrosyntheses of all groups involved, i.e. Evans, Hanessian, (Scheme I), and Lautens/Colucci, (Scheme II) illustrate this.

Both of the previously published total syntheses of ionomycin employed similar strategies. Evans and Hanessian applied identical disconnections in the construction of the ionomycin backbone; C1-C10, C11-C16, C17-C22, and C23-C32. In addition, the mode of coupling of the individually constructed fragments, and the order of coupling were identical. Different approaches to the individual subunits make each of the previous synthetic efforts distinct.
2.2 Syntheses of the C1-C9/C10 Fragment

The C9-C11 β-dicarbonyl region of (+) ionomycin is an obvious point of disconnection. Evans and Hanessian chose to make the C1-C9 fragment which could be coupled via aldol condensation of the C10 enolate to the C11 aldehyde. Colucci on the other hand, opted to construct the C1-C10 fragment, after which the C10 enolate could be coupled to the C9 aldehyde.

Once the choice of disconnections was made, the focus was turned to the stereochemically controlled installation of the syn-1,3-anti-3,5 methyl triad on the carbon backbone.

2.2.1 Evans Synthesis of the C1-C10 Fragment

A unique synthetic approach was used to introduce each of the three stereocentres of this fragment, C4, C6, and C8. First, Evans used a chiral aldol reaction developed within their laboratory. The boron enolate of the norephedrine-based chiral carboximide, 2, was added to acetaldehyde, as seen in Scheme III. This reaction proceeded highly selectively, with a diastereomeric excess exceeding 98%, and in good yield (93%) to give the β-hydroxycarbonyl, 3. Transesterification with lithium benzyloxide affected the removal of the chiral auxiliary. This ester was then reduced to the diol before Swern oxidation to the aldehyde. Reduction to the primary allylic alcohol was followed by condensation with (carbethoxyethylidene)triphenylphosphorane, to give an α,β-unsaturated ester. A second reduction led to a primary allylic alcohol which was then iodinated to give compound 4.
Next, the C4 center was established using the same propionate chiral auxiliary in an asymmetric alkylation approach, also developed in the Evans laboratory. The allylic alcohol was first converted to its corresponding allylic iodide, via Landauer-Rydon methodology using methyltriphenoxyphosphonium iodide in DMF. The alkylated product, 5, was obtained in 73% yield, with a diastereomeric excess of 96%. A final two carbon extension was performed using the same sequence outlined directly above to give the full C1-C10 backbone. Installation of the correct stereochemistry at C6 remained before completion of the fragment 6.

In order to install the correct stereocentre at C6, the C9 carbonyl was carried through the sequence as the corresponding secondary alcohol. This hydroxyl group could then be exploited in a directed hydrogenation reaction to give the requisite 1,3-syn-dimethyl relationship. Cationic rhodium catalyst, [Rh(NBD)(DIPHOS)-4]BF₄, 5 mol%, afforded the hydrogenated product in 96% yield, with a diastereomeric ratio of 94:6, favouring the desired stereochemical orientation at C6. This selectivity is assumed to arise from 1,3 strain conformational effects at the allylic position.
The C1-C10 fragment was obtained in 17 steps starting from (1S,2R)-norephedrine.

2.2.2  Hanessian Synthesis of the C1-C10 Fragment

Hanessian employed two butenolide templates, each derived from L-glutamic acid, to stereoselectively construct the C1-C10 skeleton, Scheme IV. (Phenylthio)methane provided the one remaining carbon necessary to complete the 10 carbon fragment.

The L-glutamic acid derivative, lactone 7, has a methyl group which corresponds to one of the syn-oriented methyl groups in the desired fragment. A second methyl group was necessary at the ring oxygen bearing carbon. This was seen to arise from direct nucleophilic displacement.

Scheme IV

L-Glutamic Acid

\[\begin{align*}
\text{OTBDMS} & \rightarrow \text{OH} \\
\text{Me}_3\text{Si} & \rightarrow \text{O} \\
\text{OR} & \rightarrow \text{OTBDMS} \\
\text{SPh} & \rightarrow \text{OTBDMS} \\
\text{OR} & \rightarrow \text{OTBDMS}
\end{align*}\]
Epoxide 8 was obtained from the lactone in four steps. Epoxide opening with (phenylthiomethyl)lithium assisted by DABCO\textsuperscript{9} followed by protection provided the tosylate, 9. Direct nucleophilic displacement of the tosylate, with complete inversion of stereochemistry, was affected by a sulfur assisted\textsuperscript{10} reaction with lithium dimethylcuprate.\textsuperscript{11} The presence of the sulfide proved to be pivotal. If a sulfoxide group or an alkyl group were present in lieu of the sulfide, competitive elimination resulted. Next, elimination of the thioether group was performed, resulting in a C9-C10 olefin which underwent Wacker oxidation, unselective reduction and protection to give silyl ether 10.

In preparation for a Peterson olefination with a second L-glutamic acid derivative, 11, the primary hydroxyl group was next oxidized to the aldehyde. The mixture of olefins was hydrogenated to produce the corresponding saturated lactone, 12, as a mixture of C9 epimers. The bis(phenylthio) ether was formed via the diol derived from the lactone, 13. Desulfurization using Raney-nickel gave the doubly deoxygenated product, which was then oxidized to give ionomycin fragment 14.

The Hanessian synthesis of the C1-C10 fragment of (+) ionomycin required 26 steps from the starting L-glutamic acid.
2.2.3 Colucci/Lautens Synthesis of the C1-C9 Fragment

It was noted early on that the C1-C9 fragment of ionomycin contained the 1,3-syn-3,5-anti methyl triad orientation that was obtained after methyllithium induced nucleophilic ring opening of [3.2.1] oxabicyclic alkenes followed by ozonolysis.\textsuperscript{12}

Scheme V

Monocycle 15 was obtained from nucleophilic attack (methyl lithium) at the C7 position of a well known oxabicycle\textsuperscript{13}, Scheme V. Resolution of the resulting diol proceeded by esterification with a chiral acid. The mandelate ester used served two additional purposes; to act as a protecting group, and as a hold to differentiate the two ends of the acyclic fragment after ozonolysis with reductive workup.
Ozonolytic cleavage resulted in a mixture of hydroxy lactols, 17. The primary hydroxyl was selectively protected as the silyl ether before removal of the mandelate ester, which was achieved by treatment with DIBAL-H. At this point, a two carbon extension is required to complete the 9 C backbone, and to this end, triphenylcarbo-t-butoxymethylene phosphorane was used, to yield the monoprotected triol 18.

The dideoxy product was obtained via application of Barton conditions. Formation of the thiocarbonate led only to deoxygenation at C7, and not C5: Barton had previously determined that simultaneous deoxygenation would not occur\(^{14}\) and so a sequential approach was undertaken. To accomplish the task at hand, namely the second deoxygenation, Rasmussen's protocol\(^{15}\) was applied to produce a C5 thiocarbonylinidazolidine which was then reduced. It remained for the functionality at both terminals to be adjusted. This was accomplished in three additional steps.

Treatment with TBAF resulted in deprotection of the silyl ether. Transesterification was effected by refluxing conc. H\(_2\)SO\(_4\) in methanol. Finally oxidation gave the aldehyde 19 in a total of 17 steps starting from furan, with an overall yield of 2.5\%.
2.3 Syntheses of the C10/C11-C16 Fragment
Evans and Hanessian both constructed the C11-C16 fragment of ionomycin, while the Colucci/Lautens synthesis involved the construction of a C10-C16 fragment. As with Evans and Hanessian, Colucci intended to couple the C16 and C17 termini via a Julia-Lythgoe\textsuperscript{16} reaction. All three syntheses also sought to use the same coupling to join the C1-C10 fragment to C11, or the C1-C9 fragment to C10 as the case may be: A regioselective enolization\textsuperscript{17} followed by an aldol condensation to give the desired bond formation. Three stereocenters exist in each of the two described fragments, C11, C12, and C14.

2.3.1 Evans Synthesis of the C11-C16 Fragment
In their construction of the C11-C16 fragment of ionomycin, the Evans group again used two chiral propionate enolates, Scheme VI. Cinnamyl bromide was added to the lithium enolate of 20 with 98.3:1.7 diastereoselectivity. The chiral auxiliary was removed by reduction with lithium aluminum hydride.

Scheme VI
Mesylation of the resulting primary alcohol followed by treatment with sodium iodide afforded allyl iodide $22$. Due to its greater nucleophilicity, the prolinol amide enolate was applied to the next alkylation applied, resulting in a diastereomeric ratio of 97:3. The corresponding carboxylic acid was obtained after internally assisted hydrolysis and treatment with sodium hydroxide. Less than 1% epimerization was observed upon reduction to the C11 alcohol with lithium aluminum hydride, to give $24$. This alcohol was protected before manipulation of the C16 position. Ozonolysis followed by reductive workup, provides a handle for further functionalization; formation of either the phosphonium salt or the sulfone, $25$, to participate in trans olefination through Schlosser-Wittig$^{18}$ or Julia$^{19}$ reactions.

2.3.2 Hanessian Synthesis of the C11-C16 Fragment

Hanessian began his work on ionomycin early on, as did Evans, with a paper published in 1986$^{20}$ detailing the construction of two fragments of ionomycin; C2-C10, and C11-C22, from butenolide templates. These early routes were not considered synthetically viable. In 1990, Hanessian published a synthetic route to the C11-C16 fragment$^{21}$, and it is this approach, illustrated by Scheme VII, that was later used in their total synthesis.

A series of four steps from L-glutamic acid afforded the chiral compound $26$. Conjugate addition resulted from treatment of $26$ with trithiomethyl lithium to give a diastereomeric ratio of 99:1 in favour of the desired isomer. Installation of a hydroxyl group alpha to the carbonyl was achieved by trapping of the enolate with an oxodiperoxomolybdenum (IV)-pyridine-HMPA complex$^{22}$. Raney Nickel reduction effected the removal of the three C12 thiomethyl groups.
The second butenolide template was formed in situ. The epoxide formed from 28 underwent nucleophilic attack by the sulfone anion 30 to give the hydroxy acid butenolide precursor 31. Lactone formation was accomplished by treatment with EDCI and DMAP. The sulfide was oxidized to the sulfoxide which then underwent elimination to give the butenolide. Treatment with lithiodimethyl cuprate effected the second conjugate addition which gave compound 32 with the newly installed stereocentre at C14. A further 8 steps afforded alcohol 33.

The C16 functional handle remained to be introduced. Sulfonation of 33 was accomplished by mesylation and subsequent displacement with lithium thiophenoxide. Oxidation with mCPBA yielded the targeted compound 34 in a total of 25 steps, starting from L-glutamic acid. This methylation-hydroxylation sequence is the same methodology used in the Hanessian synthesis of the C17-C22 fragment of ionomycin.
2.3.3 Colucci/Lautens Synthesis of the C10-C16 Fragment

A complete racemic synthesis of the C10-C16 fragment was achieved by Colucci in 10 steps starting from furan, with an overall yield of 10%. The more important enantiopure approach, Scheme VIII, was less direct.

Scheme VIII

The enantioselective desymmetrization developed by Rovis\textsuperscript{23} was applied to known oxabicycle 35, prepared in 3 steps from furan. Selective protection of the ring opened product as the para-methoxybenzyl ether gave cycloheptenol 36. The choice of PMB as the protecting group is accredited to it’s ability to be selectively cleaved at a later stage.
Lemiux oxidation was applied to the diprotected cyclic olefin 36, in lieu of ozonolysis which resulted in partial oxidation of the PMB group. Diol formation followed by oxidative cleavage to give the dialdehyde 37, proceeded smoothly with an overall yield of 90%.

An observation made by Tsuji in 1965 was then applied to the dialdehyde as a selective means of decarbonylation. He observed that the presence of branching alpha to an aldehyde, caused a decrease in the rate of decarbonylation using stoichiometric Wilkinson's catalyst. With this information in hand, the desired monaldehyde 38 was obtained in 78% yield over two steps. A stabilized Wittig reaction under Roush conditions provided the unsaturated sulfone 39, which was directly reduced to the saturated sulfone 40, under Raney-nickel catalysis, leaving the PMB ether intact. Deprotection of the silyl ether preceded deoxygenation under Rasmussen's conditions which afforded the target molecule 41. This piece was accomplished in 13 steps, in an impressive overall yield of 18.3%.
2.4 Syntheses of the C17-C22/C24 Fragment of Ionomycin

The C17-C22/C23 fragment consists of four adjacent stereocentres (C18, C19, C20, and C21), with alternating orientation in space.

This propionate derived molecule, having anti anti anti substitution pattern, lends itself to many synthetic approaches. Three are outlined below.

2.4.1 Evans Synthesis of the C17-C22 Fragment

Developments in the Evans laboratory showed that addition of the boryl enolate of crotylimides to aldehydes results in a syn, α-vinyl adduct. This observation was applied to install the C19 and C20 stereocentres of ionomycin with high diastereoselectivity via an aldol condensation, Scheme IX. Reaction of crotylimide 42 with (S)-0-benzyl-2-methyl-3-hydroxypropionaldehyde, to give 43 in 58% overall yield, based on the alcohol precursor to the aldehyde. The removal of the chiral auxiliary poses a problem. The competing electrophilicity of the endocyclic carbonyl moiety necessitates the activation of the exocyclic carbonyl. This is accomplished by reformation of the boron aldolate. Reaction with tri-n-butylborane and glacial acetic acid followed by reduction gives the monoprotected triol 44 with the newly corrected stereochemistry at C20. Tosylation and reduction with lithium triethylborohydride effected the deoxygenation of the methyl substituent at C20, to give olefin 45.

Application of Upjohn conditions resulted in a C21 diastereomeric mixture of C21, C22 diols. The primary hydroxyl of both diastereomers were selectively protected as the silyl ether, so that the desired 3,5-acetonide could be formed selectively. Deprotection and oxidation to the aldehyde was carried out before equilibration of the trans acetonide 49 to the thermodynamically
more stable counterpart 48. Deprotection of the silyl ether, the thirteenth and final step of this sequence, afforded syn acetonide 50, in a 98:2 equilibration mixture.

Scheme IX

2.4.2 Hanessian Synthesis of the C17-C22 Fragment

The Hanessian synthesis of C17-C22 involved the same strategy seen in their synthesis of the C11-C16 fragment, the selective methylation of two chiral butenolide templates. Here, installation of a hydroxyl functionality alpha to the carbonyl follows methylation in each case, (Scheme X). Opening of the ring, selective protection of the primary hydroxyl function, and epoxidation, installed the correct stereochemistry at C19. The method of acetate extension and replication of the butenolide template, to afford 55 is described in previous reports.
Again, conjugate addition of a methyl nucleophile was used to introduce the second methyl group. The syn product was formed exclusively. Oxidation under the previously applied conditions resulted in an epimeric mixture of alcohols at the C21 position. The unwanted diastereomer was favoured in a ratio of 1.7:1. Both diastereomers of 56 were carried through to the target aldehyde in a 5 step sequence: reduction of the lactone, formation of the primary pivalate ester, acetalization, cleavage of the pivalate esters 57 and 58, and finally Swern oxidation\textsuperscript{33} to afford aldehydes 59 and 60. The undesired enantiomer 59 was easily epimerized to the thermodynamically favoured acetal 60. It is of interest to note the application of the same equilibration strategy by the Evans group\textsuperscript{34} in their synthesis of this fragment.

The synthesis of the C17-C22 fragment was finally accomplished in 25 steps starting from L-glutamic acid.
2.4.3 Colucci/Lautens Synthesis of the C17-C23 Fragment

The work of Aspiotis\textsuperscript{35} provides us with a route to the known enantiopure dihydroxylated cycloheptenol 61. Oxidative cleavage of this monoprotected ring system affords the backbone of the C17-C23 fragment. The immediate challenges are inversion of the C21 centre, and differentiation of the dialdehyde that arises from oxidative cleavage.

![Scheme XI](image)

(a) DMSO, (COCl)\textsubscript{2}, NE\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, -78\textdegree C; (b) PhMe,DIBAL-H, -78\textdegree C; (c) THF, KHMDS, PMBCl; (d) Q, MeOH/CH\textsubscript{2}Cl\textsubscript{2}, -78\textdegree C then NaBH\textsubscript{4}, rt; (e) CH\textsubscript{2}Cl\textsubscript{2}, DDQ, Mol. Sieves, rt; (f) TrCl, NE\textsubscript{3}, DMAP, CH\textsubscript{2}Cl\textsubscript{2}, then CH\textsubscript{2}Cl\textsubscript{2}, DIBAL-H, -78\textdegree C to 0\textdegree C, then DMSO, (COCl)\textsubscript{2}, NE\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, -78\textdegree C

In response to failed attempts at a Mitsunobu reaction, a simple oxidation-stereospecific reduction sequence (DIBAL-H) effects the inversion, leading to a diastereomeric ratio >30:1 in favour of the syn alcohol. Para-methoxybenzyl protection is the final stage before reductive ozonolysis was carried out. Further reduction gives the tetrol 65.
Specific manipulation of the C17 aldehyde made use of the observation of Oikawa\textsuperscript{36} et al. Specifically, that anhydrous oxidation of the benzylic position of para-methoxybenzyl ethers will result in cyclization onto the cation if an appropriately positioned hydroxyl group exists. Treatment of 65 with DDQ in dichloromethane afforded the cyclization product, acetal 66, in 88\% yield. This elegant differentiation was followed by hydroxyl protection at \textit{C}17, and reduction of the acetal under Takano's protocol using DIBAL-H.\textsuperscript{37} Swern oxidation gave fragment 67 in 12 steps from furan, with an overall yield of 19.6\%.


13. Prepared in two steps from the cycloaddition of furan and DBK to yield the oxabicyclic ketone followed by stereoselective reduction with L-Selectride to give the axial alcohol; Brown, H. C.; Krishnamurthy, S.; J. Am. Chem. Soc. 1972, 94, 7159


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CHAPTER 3

CHEMISTRY OF THE TETRAHYDROFURANYL SUBUNIT
3. The Chemistry of the Tetrahydrofuranyl Subunit

3.1 Synthetic Developments Towards Tetrahydrofuran Synthesis

As stated by Boivin, the construction of a polyether antibiotic is, to a large extent, an exercise in the preparation of substituted oxygen heterocycles. Total synthetic efforts towards various polyether antibiotics, over the past forty or so years, has necessitated the development of new synthetic strategies towards the tetrahydrofuranyl ring system. As a result, a variety of regio, chemo, and stereoselective routes to many substituted tetrahydrofuran moieties, including the cis-2,2,5-trisubstituted tetrahydrofuranyl subunit of interest, have been put forth.

It should be noted however, that in most cases, the focus has been on the formation of disubstituted ring systems, and a large gulf remains between development and our practice, since the B ring of ionomycin is a 2,2,5-trisubstituted system.

3.1.1 Diastereoselective Epoxidation of a Bis Homoallylic Alcohol Followed by Acid Catalyzed Ring Closure

Probably the most widely used approach to tetrahydrofuran synthesis is the epoxidation of a bis homoallylic alcohol followed by acid catalyzed ring closure. A look at representative developments in this area follows.

The construction of ether rings through intramolecular attack of hydroxyl groups on epoxides, has often been applied in the total syntheses of polycyclic ethers, such as monensin, lasalocid A, and uvaricin. Consequently, the development of methodology using different parameters, such as olefin geometry, solvent, and epoxidation catalyst, to control the nature of diastereoselectivity has remained an important synthetic endeavour.
An important advance in epoxidation-cyclization methodology was reported by Kishi in 1978.\textsuperscript{7} $\alpha,\delta$-Unsaturated alcohols were treated with t-BuOOH in the presence of VO(acac), according to Sharpless' protocol. The trans 2,5-disubstituted ring product predominated in a greater than 20:1 ratio upon addition of acetic acid. Kishi invoked two transition state conformations to account for the observed selectivity, Scheme I. This Kishi transition state model, has been widely and successfully applied to both predict and explain the stereoselectivity of epoxidation-cyclization sequences.\textsuperscript{8} Determination of the favoured product is based on minimized steric congestion. Factors such as A\textsuperscript{1,3} strain, as well as the bulk, orientation and number of substituents must all be considered.

\textbf{Scheme I}

![Scheme I](image)

This newly developed methodology was applied by Kishi et al. in the first total synthesis of lasalocid A\textsuperscript{9}, Scheme II. An asymmetric epoxidation cyclization successfully formed the first trans ring. The second epoxidation proceeded, as expected, to give the trans epoxy-alcohol which, upon ring closure, would afford the trans-tetrahydrofuran. However, in this case it is the cis-ring closing that is required. Although inversion of the epoxide is possible, it is a tedious process, and another more direct route was developed.
In 1988 Nicolaou et al. sought to better define the stereospecific construction of oxirane systems, again using the Sharpless asymmetric epoxidation to give chiral materials and intramolecular epoxide opening via a primary hydroxyl nucleophile. A versatile synthetic route to monosubstituted O-heterocycles was developed.

The regioselectivity of cyclizations, whether 6-endo or 5-exo, was found to be dependant on the electronic nature of the substituent. As expected, it was found that a p-orbital adjacent to the epoxide unit activates the carbon-oxygen bond to nucleophilic attack, resulting in a 6-endo cyclization. The 5-exo cyclization predominates in the absence of a p-orbital.

After a systematic look at epoxidation-cyclization reactions, it was concluded that by varying the geometry of the allylic substrate, the stereochemistry of the epoxide and the nature of the substituent, any of the mono-substituted oxacycles, shown in Scheme III, could, to a greater or lesser degree, be formed.
Although these studies established well-defined and predictable routes to mono-substituted THF and THP systems of pre-design stereochemistry, a reliable route to higher substituted tetrahydrofuran ring systems remained elusive.

In 1990, the first total synthesis of Teurilene, a polyether containing 3 tetrahydrofuran moieties, was published by Hashimoto et al., Scheme IV.\textsuperscript{13} In this synthesis, two simultaneous vanadium(V) catalyzed oxidation-cyclization reactions were elegantly employed to form two tetrahydrofuran rings with differing stereoselectivities. Two developments were key to the stereocontrol of this approach. Firstly, Kishi’s findings that vanadium(V)-catalyzed epoxidation-cyclization of 4-substituted 4-en-1-ol systems result in an anti epoxy alcohol which cyclizes under standard acid catalysis to afford the trans 2,2,5-tetrahydrofuranyl ring. And secondly, a development in their own total synthesis of thyrsiferol\textsuperscript{14}, that under identical conditions, 5-substituted 4-en-1-ol systems form syn epoxy alcohols which cyclize to form a cis fused ring.
The desired cyclization precursor 19 was obtained after approximately 20 steps. Although arduous, the high yields make the sequence viable. Simultaneous epoxidation afforded 25% of the bis epoxide. In addition, 30% of the material underwent monoepoxidation at the 4-substituted enol to give the trans tetrahydrofuran. Tetrahydrofuran 20 could then easily be transformed into 21, resulting in an overall product yield of 56%.
over 2 steps. The third oxacycle was prepared via monomesylation of 20 at the 4-position, followed by treatment with potassium carbonate in methanol, to give teuriline, 21. Overall, this synthesis is an impressive display of stereocontrol manipulation.

3.1.2 Oxidative Cyclization of 1,5-Dienes

In 1965, Klein and Rojahn reported that upon treatment with potassium permanganate, 1,5-dienes are oxidized to substituted tetrahydrofurans in lieu of the expected tetrol. This reaction which spawns 4 new stereocentres, Scheme V, is limited to the formation of cis oxacycles, as well as by the number of available diene precursors.\(^\text{15}\)

The search for workable routes to polyether antibiotics in the late 1970's caused a renewed interest in this methodology. Klein and Rojahn explored a very limited number of substrates, only those structurally similar to geraniol and nerol. Walba et al. expanded the applications by looking at the extent of stereospecificity in unsymmetrically substituted olefinic carbons.\(^\text{16}\) In all cases complete stereospecificity was maintained leading both Walba and Baldwin, who was doing parallel research\(^\text{17}\), to posit mechanisms to explain the phenomena.
3.1.3 **Oxabicyclo[3,2,1]octenones**

The variety of synthetic pathways to [3,2,1] oxabicycles is extensive.\(^\text{16}\) The most common method is probably the stereospecific addition of oxoallyl cations to furans through an endo, boat-like transition state, with the oxoallyl cation adopting the W conformation.\(^\text{19}\) Due to the ease and versatility of large scale production of the starting cycloadduct, the use of these oxabicycles is particularly attractive. The formation of 2,5-substituted tetrahydrofurans is just one of the many synthetically valuable applications of [3,2,1] oxabicyclic ketones, developed in this lab and others.

**Scheme VI**

One approach involves treatment of the oxabicycle to Bayer-Villager conditions. The resulting lactone can then be hydrolyzed to give a 2,5-substituted tetrahydrofuran. In 1975, White and co-workers synthesized (\(\dagger\))-nonactic acid, a macrocyclic antibiotic with biological activity as a potassium ionophore by this route (Scheme VI).\(^\text{20}\) Also notable is the work by Noyori et al., in preparing the first 2,5-disubstituted ribo-C-nucleosides, published in 1980.\(^\text{21}\) Previous work in this area had applied manipulation of readily available carbohydrates, but Noyori sought stereocontrolled precursors from bicyclic ketones.\(^\text{22}\) Oxidation of the double bond of the oxabicycle to give the diol affords a ribose skeleton upon \(\alpha\)-cleavage. In 1982, Hoffman et al., used this same methodology in their synthesis of lilac alcohol.\(^\text{23}\)
Molander arrived at the 2,2,5-tetrahydrofuranyl unit with the relative stereochemistry of ionomycin by applying a Bayer-Villiger oxidation to a [3,2,1] oxabicycle, followed by stereocentre manipulation and transesterification. Treatment with m-CPBA and NaHCO₃ afforded the lactone in 67% yield (89% based on recovered starting material), which, after functional group manipulation, was reduced to yield a tetrol tetrahydrofuran, 31 (Scheme VII). A notable advantage of this route is the ability to incorporate substituents directly onto the THF ring, using a substituted dicarbonyl precursor.

**Scheme VII**

An alternative to α-cleavage of the carbonyl, is the Beckmann rearrangement of the cycloadduct, seen in (Scheme VIII). This method again provides a 2,5-substituted tetrahydrofuranyl moiety. With the advent of controlled cleavage of [3,2,1] oxabicycles, another route to natural products presents itself.

**Scheme VIII**
3.1.4  Halocyclization

Bartlett et al. found that γ,δ-unsaturated alcohols, and ether derivatives cyclize at 0°C with iodine in acetonitrile. The stereoselectivity of this reaction is dependant upon the nature of the oxygen; a free hydroxy cyclizes to form a trans-2,5-tetrahydrofuran, while the corresponding O-alkylated product produces a cis substituted ring. The difference in stereoselectivity can be accounted for by the steric bulk of the oxygen protecting group, non-bonding interactions must be minimized in each case. To date, this approach has not been applied in a synthesis of (+)-ionomycin.

3.1.5  Polyepoxide Cyclization

Another approach to polyether antibiotics is one developed by Westley and Cane in their examination of the biosynthesis of ionophores. They proposed that in vivo synthesis occurs via simultaneous epoxidation of the ene moieties followed by epoxide opening. With this approach, it is the construction of a backbone containing necessary stereocentres, that presents the largest challenge. Ideally, stereoselectivity can arise from chirality residing in the chair, instead of hydroxyl group directed epoxidation. This approach was explored in the synthesis of monensin B, Scheme IX. By X-ray analysis, the two trisubstituted epoxides have the stereochemistry required for monensin B, while the third epoxide is epimeric. Although the desired fragment was not reached, it is evident that with fine tuning this synthetic strategy could prove to be very powerful, having many potential applications.
3.1.6 Miscellaneous Routes to Tetrahydrofurans

While the above described routes to tetrahydrofurans give an idea of the synthetic developments to this point, it is by no means a complete list. Further examples are mentioned here.

In her report on synthetic routes to 5/6 membered oxacycles, and spiroketals, Boivin described examples of each of the following: ring contraction of tetrahydropyrans, ester enolate Claisen rearrangement, mercuricyclization and cyclization of 1,4-diols. One more example involves the substitution at the 2 and 5 positions of a furan followed by catalytic hydrogenation which proceeds to give a single cis stereoisomer.
3.2 Synthetic Developments Towards the Tetrahydrofuran Moiety of (+)Ionomycin

3.2.1 Wuts

In their synthesis of the tetrahydrofuranyl subunit of (+) ionomycin published in 1984\textsuperscript{32}, Wuts et al. initially planned to apply the Sharpless Asymmetric Epoxidation\textsuperscript{33} to a geraniol acetate backbone. It was thought that all necessary chirality could be introduced and that the desired relative stereochemistry could be easily manipulated via a series of controlled epoxide opening reactions.

Scheme X

![Scheme X](attachment:image.png)

(a) SeO\textsubscript{2}, t-BuOOH, salicylic acid; (b) TBS\textsubscript{Cl}, DMF, imidazole; (c) MeOH, K\textsubscript{2}CO\textsubscript{3}; (d) n-BuLi, TsCl, THF; (e) LiEt\textsubscript{3}BH; (f) n-BU\textsubscript{4}NF; (g) Ti(O-Pr)\textsubscript{4}, (+)-diethyl-(L)-tartrate, t-BuOOH; (h) PhNCO, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}; (i) HClO\textsubscript{4}, H\textsubscript{2}O, CH\textsubscript{3}CN; (j) mCPBA; (k) VO(acac)\textsubscript{2}, t-BuOOH, AcOH

The transformation, (Scheme X), began with allylic oxidation, which served two purposes, firstly to provide the substrate necessary for the SAE, and secondly to serve as an attachment point from which to build the ionomycin skeleton. The correct oxidation state at C32...
was achieved early on in a one pot reaction by removal of the acetyl group, and reduction of the resulting hydroxyl group. Removal of the remaining protecting group and Sharpless Asymmetric Epoxidation afforded the desired chiral epoxide. As planned, the centers at C25, C26 and C27 were achieved by acid catalyzed opening of the epoxide. Epoxidation with $m$-CPBA and ring closure proceeded with little stereoselectivity.

Scheme XI

\[
\begin{align*}
\text{(a) Ti(O-i-Pr)}_4, (-)\text{-diethyl-D-tartrate, } & \text{t-BuOOH; (b) PhNCO, Et}_3\text{N, CH}_2\text{Cl}_2, \text{PCl}_5; \\
\text{(c) K}_2\text{CO}_3, \text{MeOH, Dowex H}^+; (d) \text{TsCl, pyridine, 0}^\circ\text{C; (e) Nal, 2-butanone; (f) Bu}_3\text{SnH, AIBN, EtOH; (g) Bu}_2\text{PH}_2\text{SiCl, DMF, imidazole; (i) LiAlH}_4; (k) K}_2\text{CO}_3, \text{MeOH; (l) CH}_2=\text{CHCH}_2\text{-MgCl, THF, room temperature} }
\end{align*}
\]
As predicted following Kishi's transition state models, the use of VO(acac)$_2$ resulted in a 20:1 ratio, favouring the wrong isomer. At this stage the problem of selectivity might be overlooked, but the inability to separate the two isomers formed forced a new approach, Scheme XI.

The C32 hydroxyl group was then realized to be potentially invaluable in directing the chirality of the epoxide. An ideal scenario involves the selective opening of a bisepoxide at the right-hand epoxide before an internal hydroxyl group affects an opening of the left-hand epoxide to afford the desired furan.$^{34}$ In actuality, the required selectivity could not be achieved and a much less elegant procedure, involving the formation and opening of one epoxide, and then the other, was initiated. The final sequence, features the following steps; asymmetric epoxidation, formation of the phenyl urethane, conversion to the cyclic carbonate via perchloric acid, protection, base-catalyzed hydrolysis of the acetate, deprotection followed by a second asymmetric epoxidation, and finally a Lewis acid catalyzed cyclization. With the successful completion of the tetrahydrofuran successfully formed, the target molecule was then easily prepared.

While the desired ring closure was achieved in 6 steps, this alternative route features many redundant functional group manipulations before the left quarter of ionomycin was obtained. In total, 14 transformations, with an overall yield of 6% were required.
3.2.2 Spino & Weiler

Spino and Weiler took a different approach to the tetrahydrofuran subunit of ionomycin, taking advantage of earlier advances made in the oxidative cyclizations of 1,5-dienes by Klein and Rojahn.\textsuperscript{35} Namely, that 1,5-dienes such as geranyl acetate, and neryl acetate, could be induced to undergo cyclization to give a cis-tetrahydrofuran product.\textsuperscript{36} Further advances by Walba et al.\textsuperscript{37} showed that the stereochemistry of the resulting disubstituted oxacycle was dependant on the geometry of the diene starting material (Scheme XII).

The required diene was prepared stereospecifically in 8 steps as seen in Scheme XIII, applying methodology recently developed in the Weiler group.\textsuperscript{38} The selective formation of the E-enolate followed by formation of the E-enol phosphate by trapping with diethylchlorophosphosphate gives the Z-alkene upon treatment with a magnesium cuprate. A second dianion alkylation and enol-phosphate cuprate coupling affords the 1,5-diene 64. Oxidative ring formation proceeds to give >95% of one isomer, assumed to be the cis product based on Walba’s work, in 53% isolated yield.
Reduction of the ester group and tosylation, followed by a hydridic displacement of the tosyl group affected the deoxygenation. At this stage, a resolution was performed, (attempts to separate the isomers at an earlier stage had met with little success). Compound 66 was condensed with mandelic acid and the diastereomers were separated by flash chromatography. The resolving group was then hydrolyzed. Protection followed by conversion to the phosphonium salt completed the synthesis of the tetrahydrofuran fragment.

Scheme XIII

(a) NaH, n-BuLi, THF, O°C to rt, then MOMO-CH₂CH₂Br; (b) TEA, DMAP, HMPA, CIPO(OEt)₂, -20°C to rt; (c) MeMgCl, MeLi, CuI, THF, -45°C; (d) Dibal, O°C; (e) PPh₃, CBr₄, CH₂Cl₂, -78°C to rt; (f) -CH₂COCH-COOMe, THF, O°C to rt; (g) KMnO₄, acetone/H₂O, CO₂, -25°C; (h) LAH, THF, O°C; (i) TsCl, pyridine, O°C; (j) LAH, THF, heat; (k) (S)-(−)-O-acetylmandelic acid, DCC, DMAP, CH₂Cl₂, O°C, chromatographic separation
The overall transformation was accomplished in a series of 19 steps, many of which had unreported yields. The lengthiness of the route coupled with the undesirable formation of a racemic product that was kinetically resolved at a very late stage, prove to be significant limitations to this synthetic effort of Spino and Weiler.

3.2.3 Evans

In 1990, Evans published his asymmetric total synthesis of ionomycin. The C22-C23 bond was planned to be a point of disconnection, fixing the C23 stereocentre upon subunit assemblage. With this skeletal breakdown, the tetrahydrofuranyl subunit of interest extended from C23 to C32. The addition of the boryl enolate of 12 and the aldehyde illustrated in Scheme XIV, provided the 10 carbon framework, utilising Evans chiral auxiliaries to direct the stereochemistry at C27.

To form the oxacycle, Evans applied the Sharpless VO(acac)$_2$ epoxidation, resulting, as expected by Kishi, and later Wuts, in a 4:1 selectivity for the wrong diastereomer. Although attempts were made to invert the stereochemistry, their lack of success forced an unselective epoxidation with $m$-CPBA. This course of action was deemed acceptable due to the high chemical yield and ease of separation of the two diasteromers. Epoxidation and acid catalyzed cyclization with the hydroxyl group at C27 acting as an internal nucleophile was accomplished before attention was directed to the chirality at C26.
Lactonization which, in addition to removing the chiral auxiliary, provides an intermediate, that will readily lead to the desired decarboxylated product. Tebbe methylenation, acid catalyzed isomerization to the more thermodynamically stable internal enol, and ozonolysis followed by reductive workup, gives a C26 carbonyl group which can then undergo diastereoselective nucleophilic addition. Simple functional group manipulations gave the final
group which can then undergo diastereoselective nucleophilic addition. Simple functional group manipulations gave the final C23-C32 subunit as a phosphonium salt which could easily be transformed into the corresponding ylide to be used in the appending of subunits. An overall yield of 9% over 11 steps was achieved.

3.2.4 Hanessian

Hanessian's total synthesis of (+) ionomycin, seen in Scheme XV, was received for publication less than one month after Evans' total synthesis, (although initial work was published by R. Dow in a 1985 Ph.D. thesis). Both syntheses featured a similar approach to the tetrahydrofuranyl ring system. The epoxidation-cyclization motif was once again applied, again with hopes of stereocontrol. Hanessian chose to use an optically active epoxide, and like Wuts, geraniol, to form the skeleton of the C23-C32 chain. The terminal 2-methylpropenyl group would be cleaved at a later time to give

![Scheme XV](image)

(a) (D)-Diisopropyl tartrate, Ti(OiPr)₄, TBHP, CH₂Cl₂, 4 Å sieves, -20°C, 30 h, then Me₂S, -20°C, 62%; (b) 1. EtMgBr, THF, then add Li anion of 86, THF-HMPA, -78°C to -25°C, 18 h, 71%; (c) 1. O₃, then excess NaBH₄, MeOH, -78°C to -25°C, 3h, 87%; 2. Ac₂O, Et₃N, catalyst DMAP, CH₂Cl₂, O°C, 0.5 h, 62% overall; 3. Na, liquing NH₃, -33°C, 69%; (d) 1. TBHP, VO(acac)₂, 3 Å sieves, hexanes 24 h, 94%; (e) 1. LiAlH₄, ether, -25°C, 20 min, 86%; 2. PPh₃, imidazole, 12, CH₂Cl₂, 91%
Next, the use of the sulfone anion of geraniol in the presence of one equivalent of ethyl magnesium bromide was explored. The coupling proceeded to give a mixture of two separable diastereomers, in 41 and 30% yields. Since the sulfone functionality was removed by reduction with sodium in liquid ammonia after protection and ozonolysis, both diastereomers were carried through.

With the backbone constructed, the next challenge was stereocontrolled ring closure to form the cis trisubstituted tetrahydrofuran. The VO(acac)_2 catalyzed epoxidation-cyclization sequence pursued by Wuts and Evans was again explored, this time with an impressive degree of success. Whereas Wuts, Evans and Kishi, attempted this cyclization with a secondary hydroxyl group as the internal nucleophile, the substrate that Hanessian presented involved attack at the epoxide by a tertiary hydroxyl group. Under optimized conditions it was found that the less polar the solvent, the greater the stereoselectivity, culminating in a ratio of 9:1 cis:trans, when hexanes were used. Yields were consistently between 70 and 80%, with preference for cis decreasing to 4-5:1 with other solvents such as dichloromethane, toluene or benzene. Three simple functional group manipulations give the requisite cis-disubstituted tetrahydrofuran subunit in a total of 10 steps with an overall yield of 7%.

For the sake of comparison, the original transition state models proposed by Kishi applied to the tetrahydrofuran precursors are illustrated below, (Schemes XVI-XVIII). The observed selectivity in each of the three scenarios is made apparent.
Scheme XXI: Wuts Transition States

Scheme XVII: Evans Transition States

Scheme XVIII: Hanessian Transition States


23. Rabe, S. Diplomarbeit, Universitat Hannover, 1982


38. (a) Sum, F. W.; Weiler, L. Tetrahedron, 1981, 31 Supp 1, 303; (b) Alderdice, M.; Spino, C.; Weiler, L. Tetrahedron. 1984, 25, 1643


CHAPTER 4

OUR SYNTHESIS

OF THE C24-C32 FRAGMENT OF

(+) IONOMYCIN
4 Introduction

4.1 Synthetic Strategy and Discussion of the Route

The following synthetic route to the C24-C32 subunit of (+) ionomycin was developed by John Colucci in the Lautens group. In designing this sequence, Colucci considered several important factors, such as installation of appropriate stereocenters at C31 and C26, functionality at C24 suitable to allow easy appendage to the neighbouring subunit, length of route and of course achieving a ring closure with the required absolute stereochemistry. Previous synthetic efforts towards the tetrahydrofuranyl subunit of ionomycin have provided invaluable information, which was incorporated into the development of the strategy described below.

The retrosynthesis, shown in Scheme I, illustrates the key transformation en route to ionomycin. The skeleton of this subunit is derived from geranyl acetate, which, although one carbon short of the desired 9 carbon chain, has inherently correct positioning of the two methyl groups, as well as olefin moieties which can be functionalized. The architecture of geraniol has proven to be an excellent point of departure in many previous syntheses of polyether antibiotics, including ionomycin, as mentioned earlier.2
First, selenium catalyzed allylic oxidation\(^3\) of the geranyl acetate starting material, using a tert-butyldihydroperoxide co-oxidant, was performed in order to functionalize the carbon destined to be C25. It was anticipated that the addition of a methyl-phenyl-sulfone anion to this centre would provide not only the missing carbon atom, but an appropriate linkage precursor. The ease of formation of the sulfone anion makes it ideal for nucleophilic attack to the planned aldehyde at C23 via a Julia-Lythgoe reaction\(^4\) to give an E-olefin, which could then be used in the construction of the A ring. Of equal importance is the assumed ease with which the sulphone moiety could be removed following attachment.\(^5\) Eventually, cleavage was effected by oxidation of the coupled C17-C23 and C24-C32 fragments, followed by reduction with SmI\(_2\). Another foreseen advantage of this approach was the ability to exploit the penchant of sulfone anion to attack carbonyls. A greater number of anion equivalents could cleave the acetate, via nucleophilic attack, leaving a free hydroxyl group to act as a handle for the planned Sharpless asymmetric epoxidation to follow.

In order to attach the methyl-phenyl-sulfone, the existing hydroxyl group was first converted to the bromide iii. At this point simple nucleophilic displacement by the sulfone anion, formed by the addition of butyllithium to phenyl methyl sulfone in THF at 0°C, afforded iv in 65\% yield, along with the dimer as an undesired side product. The common problem of dialkylation of sulfone-stabilized carbanions, was investigated by by Pine et al..\(^6\) The assumed mode of action is deprotonation of the mono-alkylated product, Scheme II. The resultant anion then acts as the new nucleophile to displace the bromide on the second C24-C32 chain.
The division between mono and polyalkylated product is believed to be under thermodynamic control. Although the monosubstituted sulfone is alkylated much more readily than the unsubstituted precursor, the monoalkylated anion is thermodynamically less stable than the phenyl-methyl-sulfone anion.

The possibility that aggregation about the lithium cation could come into play was also considered by the Pine group. If this were the case, aggregation would increase as the bulk of the substrate decreased, reducing the likelihood of alkylation. Obviously, the unalkylated iii is less sterically congested than the corresponding monoalkylated product, iv. Since it is known that the degree of ion association decreases with potassium in relation to lithium, a change in counterion should result in an increase in monosubstituted product. Pine found this to be true as the base was switched from butyl-lithium to potassium hydride.

Unfortunately, in our case, such a change in base did not result in any degree of improvement in the ratio of mono to dialkylated product. Other variables that were examined without success include; temperature, rate of addition, the number of equivalents
phenyl sulfone relative to base, and the order of addition. Colucci on the other hand, did not report dialkylation products in the original experimental work.

The Sharpless asymmetric epoxidation, which has proven to be of pivotal import in the previous syntheses of both ionomycin and tetrahydrofuran rings, was next applied. Colucci found that with substrate iv, the catalytic version of the Sharpless asymmetric epoxidation\(^6\) resulted in a decrease in both the yield and stereoselectivity of the reaction. This compromise could not be made and allylic alcohol iv was subjected to stoichiometric amounts of (+)-diisopropyltartrate, titanium isopropoxide and tert-butylhydroperoxide. Under these conditions, the enantiomeric excess was found to be >97\% by Mosher’s ester analysis.\(^9\) Our results were in full agreement with this analysis.

It is important to note that a proper workup was found to be critical to the yields of this reaction. As proposed by Sharpless, a solution of ferrous sulfate and tartaric acid was used to break down the titanium isopropoxide. The resulting titanium salts could then be removed by separation of the aqueous layer. If a trace of Lewis acidic titanium remained, the epoxide v was found to decompose at an alarming rate, especially upon concentration.

Next, the epoxide had to be manipulated into the necessary precursor for the cyclization-epoxidation reaction. Tosylation of the epoxy-alcohol proceeded without event. This relatively unstable molecule vi, was then directly subjected to acid catalyzed opening of the epoxide to form a monotosylated triol. Here, stereospecific bimolecular nucleophilic attack occurred at the tertiary centre, resulting in an inversion of stereochemistry. This backside attack was required to achieve the correct relative
and absolute orientation of stereocentres. Selective protection of the secondary hydroxyl of viii as the tert-butyldimethylsilyl ether was the final step in preparation for the ring formation.

The approach decided upon followed Hanessian's beautifully laid path. We similarly pursued a substrate directed epoxidation, followed by acid catalyzed cyclization of a 5-substituted-4-en-l-ol. In this case however, a problem of solvent was encountered. The use of hexanes as described by Hanessian was not a possibility due to insolubility. A solution of 3:1 heptanes to dichloromethane was finally found to be suitable, resulting in the best selectivity, while maintaining solubility. Catalytic amounts of VO(acac)₂ and 4 equivalents of the co-oxidant, tert-butylhydroperoxide, were added to the substrate solution twice, at a 12 h interval. After this period, a catalytic amount of pyridinium para-toluenesulfonate was added to aid the ring closure. A final ratio of 7.8:1 cis/trans was obtained, rivaling Hanessian's own 9:1. The two isomers, ix along with its counterpart, were carried through the synthesis together, the separation to be performed at a later stage.

The deoxygenation at C32 of ix next presented itself. Direct nucleophilic hydride displacement was impossible due to the incompatibility of the sulfone group, which suffered various degrees of reduction as well as displacement. Conversion to the iodide followed by a radical based reduction lead to the desired reduced product. The displacement of the tosylate was carried out in 2-butanone, facilitated by the presence of 18-c-6, to give x. The diastereomeric tetrahydrofuran mixture was then deiodinated under standard radical conditions, refluxing toluene, tributyltin hydride and AIBN as the radical initiator. It was at this point that separation of the two diastereomers could be accomplished.
The quality of tributyltin hydride was found to be of the utmost importance. Any degree of contamination could result in decomposition of the valuable starting material, lowering the yield from 91% which was possible under optimum conditions.

The final step in the sequence of the C24-C32 chain was the protection of the hydroxyl group in \( \text{xi} \) as the labile trimethylsilyl ether, using the corresponding triflate at \(-78^\circ\text{C}\). The fragment \( \text{xii} \) could then be coupled as prescribed to the other subunits.
4.2 EXPERIMENTAL

All glassware was flame dried under nitrogen gas and cooled before use. Solvents and solutions were transferred with syringes and needles or canulae under standard inert atmosphere techniques.

THF and toluene were distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from calcium hydride before use.

Both $^1$H NMR, and $^{13}$C NMR spectra were recorded at a 400 MHz Varian XL400 spectrometer with CDCl$_3$ as reference standard ($\delta=7.24$ ppm for $^1$H NMR, and $\delta=77.0$ ppm for $^{13}$C NMR). Spectral features are tabulated in the following order: chemical shift ($\delta$, ppm); number of protons; multiplicity (s-singlet, d-doublet, t-triplet, q-quartet, qn-quintet, sp-septet, m-complex multiplet, br-broad); coupling constants ($J$, Hz). $^{13}$C NMR were recorded at 50 or 100 MHz.

Gas chromatography was performed on a Hewlett Packard 5890 gas chromatograph using an HP-20 carbowax column, and chiral column $\beta$-TA and $\gamma$-TA. Analytical TLC was performed using EM Separations precoated silica gel 0.2 mm layer UV 254 fluorescent sheets. Column chromatography was performed as "Flash Chromatography" as reported by Still$^{11}$ using (200-400 mesh) Merck grade silica gel.

Phenyl-methyl-sulfone was prepared in a procedure described by Trost, by oxidation of phenyl methyl sulfide.$^{12}$

Since the $^1$H NMR and $^{13}$C NMR data obtained was in full agreement with previous experimental data, no further characterization was performed. For IR, $[\alpha]_D$ and HRMS data, see Ph D thesis of John Colucci, University of Toronto, 1997.
[2E,6E]-Acetic acid 8-hydroxy-3,7-dimethyl-octa-2,6-dienylester

To a solution of salicylic acid (3.52 g, 25.5 mmol), selenium dioxide (565 mg, 5 mmol), and tert-butyl hydroperoxide (127 mL 70% solution in water, 917 mmol) in 90 mL dichloromethane, was added geranyl acetate (50 g, 255 mmol) at 10°C, as prescribed by Sharpless. The resulting solution was stirred at room temperature for 48 h. At this point dimethyl sulfoxide (50 mL, 917 mmol), and 200 mL of water were added to the reaction. The aqueous phase was separated, extracted with ether (3 x 200 mL), dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by flash chromatography (10-40% ether/hexanes) on silica gel gave known compound ii as a yellow oil (28.2 g, 52%)
[2E,6E]-Acetic acid 8-bromo-3,7-dimethyl-octa-2,6-dienylester

\[
\text{OH} \quad \text{OAc} \quad \text{Br} \quad \text{OAc}
\]

N-bromosuccinimide (21.5 g, 121 mmol) was added to a solution of alcohol ii and triphenylphosphine\(^\text{ii}\) (32.6 g, 124.4 mmol) in 225 ml of dichloromethane stirring in a cryobath at -20°C. The solution was stirred at -20°C for 2.5 h. In vacuo concentration to eliminate solvent and flash chromatography of resulting orange residue (5-10\% ether/hexanes on silica gel) gave the known allyl bromide iii\(^\text{iii}\) (23.76 g, 76.5 \%) as a yellow oil.
To a solution of methyl phenyl sulfone (43.8 g, 280 mmol) in 560 ml THF at 0°C, was added n-butyl lithium (112.3 ml, 280 mmol) via cannula. The resulting yellow precipitate was stirred for 30 min at 0°C and 1 h at room temperature. The reaction mixture was cooled to ~20°C and allyl bromide iii (16.5 g, 60.1 mmol), in 120 ml of THF was added slowly via cannula, over a period of 30 minutes. The solution was stirred for 2 h as the cooling bath gradually warmed to room temperature. Saturated NH₄Cl solution, (200 ml of), was added to the yellow solution. After vigorous shaking, the aqueous layer was separated, and extracted with ethyl acetate (3 x 250 ml) and CH₂Cl₂ (1 x 200 ml). The combined organic extracts were dried over anhydrous MgSO₄ and concentrated in vacuo. Flash chromatography on silica gel (30-80% ether/hexanes) gave the sulfone iv as a pale yellow oil (12.03 g, 65%).

¹H NMR (400 MHz, CDCl₃) δ 7.90-7.50 (5H, m), 5.34 (1H, t, J=7.0Hz), 5.09(1H, t, J=6.6 Hz), 4.1 (1H, m), 3.13 (2H, m), 2.32 (2H, m), 2.10-1.90 (4H, m), 1.61 (3H, s), 1.5s (3H, s), 1.41 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ 139.0, 138.8, 133.6, 130.9, 129.2, 128.0, 126.4, 123.6, 59.2, 55.0, 39.0, 32.2, 26.1, 16.2, 15.9.
To a solution of (+)-diisopropyltartrate (5.9 mL, 27.6 mmol, distilled and kept under vacuum) and crushed molecular sieves (1 g) in 225 mL dichloromethane at -20°C (cryobath), was added titanium isopropoxide (7.8 mL, 25.8 mmol, freshly distilled), according to Sharpless protocol. The resulting solution was stirred for 20 min followed by slow addition of sulphone iv (7.9 g, 25.8 mmol) in 55 mL dichloromethane and crushed molecular sieves (0.79 g) via cannula. This solution was again stirred for 20 min before addition of tert-butyl hydroperoxide that had been pre-dried over 3 Å molecular sieves for 30 min. After stirring overnight (14 h), at -20°C, the reaction was warmed to 0°C. A solution of tartaric acid (58.6 g, 390 mmol) and ferrous sulfate (170 g, 611 mmol) in 1.25 L of distilled H₂O was prepared and cooled to 0°C. The reaction mixture was slowly poured into the stirring aqueous solution. After stirring for 10 min, the aqueous layer was separated and extracted with ether (2 x 75 mL). The combined organic extracts were once again cooled to 0°C, and 130 mL of a precooled solution (0°C) of 30% NaOH in saturated brine was added. The biphasic solution was stirred vigorously for 1 h at 0°C before separation and extraction of aqueous phase with ether (3 x 100 mL) and dichloromethane (1 x 100 mL). Purification by flash chromatography on silica gel (30-50% ethyl acetate/hexanes) gave epoxy alcohol v (5.73 g, 69% yield). Analysis by gas
chromatography revealed an enantiomeric excess of approximately 95%. This is in agreement with earlier experimental results.\textsuperscript{18}

$[\alpha]_0 = +7.2^\circ \ (c=2.0, \ \text{CHCl}_3)$; $^1\text{H NMR (400 MHz, CDCl}_3) \delta 7.88-7.45 \ (5\text{H, m}), 7.11 \ (1\text{H, dt, } J=0.7, 7.0 \text{ Hz}), 3.77 \ (1\text{H, dd, } J= 4.8, 12.1 \text{ Hz}), 3.67 \ (1\text{H, dd, } J=6.6, 12.1 \text{ Hz}), 3.15 \ (2\text{H, m}), 2.92 \ (1\text{H, dd, } J=4.8, 6.6 \text{ Hz}), 2.37 \ (2\text{H, m}), 2.03 \ (2\text{H, m}), 1.72 \ (1\text{H, m}), 1.61 \ (1\text{H, ddd, } J=6.6, 8.1, 13.6 \text{ Hz}), 1.55 \ (3\text{H, s}), 1.46 \ (1\text{H, ddd, } J=7.3, 9.2, 13.9 \text{ Hz}), 12.6 \ (3\text{H, s}); \ ^{13}\text{C NMR (100 MHz, CDCl}_3) \delta 139.0, 138.8, 133.6, 130.9, 129.2, 128.0, 126.4, 123.6, 59.2, 55.0, 39.0, 32.2, 26.1, 16.2, 15.9.$
[2R,3R,3(3E)-Toluene-4-sulfonic acid 3-(6-benzenesulfonyl-4-methyl-hex-3-enyl)-3-methyl-oxiran-2-ylmethyl ester

The epoxy alcohol v (5.3 g, 16.24 mmol) was dissolved in 30 mL of dichloromethane and stirred at -10°C. To this solution was added pyridine (2.2 mL, 27.1 mmol) and freshly recrystallized para-toluenesulfonic chloride (5.2 g, 27 mmol). This solution was stirred for 48 h before a second addition of pyridine (0.22 mL) and para-toluenesulfonic chloride (0.52 g). After 1 h, 100 mL of water was added and the aqueous layer was separated and extracted with dichloromethane (3 x 200 mL). The organic extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography on silica gel (10-40% ethyl acetate/hexanes) gave tosylate vi (7.3 g, 93%) as a pale yellow oil.

\(^1\)H NMR (400 MHz, CDCl₃) δ 7.88-7.30 (5H, m), 4.09 (1H, dd, J=11.1, 5.5 Hz), 4.05 (1H, dd, J=11.1, 5.9 Hz), 3.13 (2H, m), 2.94 (1H, dd, J=5.9, 5.5 Hz), 2.44 (3H, s), 2.36 (3H, s), 1.98 (2H, q, J=7.7 Hz), 1.60-1.38 (4H, m), 1.53 (3H, s), 1.17 (3H, s); \(^{13}\)C NMR (100 MHz, CDCl₃) δ 145.0, 138.9, 133.6, 132.5, 131.6, 129.8, 129.1, 127.9, 127.8, 125.5, 68.4, 60.7, 58.6, 54.8, 37.4, 32.1, 23.3, 21.6, 16.6, 15.9.
[2R,3S,6E]-Toluene-4-sulfonic acid-9-benzenesulfonyl-2,3-dihydroxy-3,7-dimethyl-non-6-enyl ester

To a room temperature solution of tosylate vi (16.48 g, 34.5 mmol) in 170 mL of a 3:1 THF/H₂O solution was added perchloric acid (0.67 mL, 70% aqueous solution). The reaction mixture was then heated at reflux (70°C) for 3 h. The solution was cooled to room temperature before addition of saturated aqueous NH₄Cl solution (200 mL). The aqueous layer was separated and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo before purification by flash chromatography on silica gel (20-50% ethyl acetate/hexanes). Diol vii was obtained (12.2 g, 72%) as a pale, milky, oil.
[2R,3S,6E]-Toluene-4-sulfonic acid-9-benzenesulfonyl-2-((1,1-dimethylethyl)dimethylsiloxy)-3-hydroxy-3,7-dimethyl-non-6-enyl ester

To a solution of diol vii (12.2 g, 24.6 mmol) in 43 mL of dichloromethane at -20°C, was added 2,6-lutidine (6.6 mL, 59 mmol). The solution was stirred for 10 min at -20°C before slow addition of tert-butyldimethylsilyl trifluoromethanesulfonate (6.6 mL, 29 mmol). The solution was stirred at -20°C for 1 h, after which it was warmed to 0°C. 120 mL of saturated NH₄Cl solution was added. The aqueous phase was separated and extracted with dichloromethane (3 x 150 mL). The combined organic extracts were washed with 120 mL of 0.5 M HCl solution, and 120 mL of saturated brine solution. The aqueous washes were then extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel (20-70% ethyl acetate/hexanes) gave the silyl ether viii (10.9 g, 73%) as a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 7.88-7.3 (9H, m), 5.07 (1H, t, J=7.3 Hz), 4.21 (1H, dd, J=10.3, 3.3 Hz), 3.82 (1H, dd, J=10.3, 3.3 Hz), 3.66 (1H, dd, J=10.3, 3.3 Hz), 3.66 (1H, dd, J=7.3, 2.9 Hz), 3.15 (2H, m), 2.44 (3H, s), 2.36 (3H, s), 1.98 (3H, m), 1.54 (3H, s), 1.24 (1H, m), 1.08 (3H, s), 0.85 (9H, s), 0.08 (3H, s), 0.06 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ 144.9, 139.0, 133.6, 131.1, 129.8, 129.2, 128.0, 127.9, 126.6, 126.5, 76.8, 73.5, 71.1, 54.9, 37.0, 32.2, 25.9, 23.1, 21.8, 21.7, 18.1, 15.9, -4.0, -4.9.
[2R,2(2S,5R,5(1S))] Benzenesulfonic acid 2-[(5-(3-benzenesulfonyl-1-hydroxy-1-methyl-propyl)-2-methyl-tetrahydro-furan-2-yl)-2-(1-((1,1-dimethylethyl)dimethylsiloxy)-ethyl ester

Vanadyl acetylacetonate (313 mg, 1.2 mmol) and 4A molecular sieves were added to a solution of silyl ether viii (4.8 g, 7.9 mmol) in 48 mL of 3:1 heptanes/CH$_2$Cl$_2$. The green solution is stirred for 30 min after which tert-butyl hydroperoxide (2.86 mL of a 5.5 M solution in decane, 15.71 mmol), which had been predried over molecular sieves for 30 min, is added dropwise. The dark purple solution is stirred for 12 h. At this time, the solution is a brick red, and a second addition of vanadyl acetylacetonate and tert-butyl hydroperoxide (313 mg, and 2.86 mL respectively) is made to regenerate the purple colour. After another 12 h, pyridinium para-toluensulfonate (200 mg, 0.8 mmol) is added. After 4 h of stirring, the reaction mixture is purified directly by flash chromatography on silica gel (20-50% ether/hexanes). An inseparable mixture of cis ix, and trans products (3.5 g, 71%) are obtained as a pale yellow oil in a ratio of cis to trans, 7.7:1.

$^1$H NMR (400 MHz, CDCl$_3$)δ 7.88-7.30 (9H, m), 4.50 (1H, dd, $J$=10.6, 1.8 Hz), 3.78 (2H, m), 3.67 (1H, dd, $J$=7.3, 1.5 Hz), 3.36 (1H, ddd, $J$=16.8, 12.5, 4.4 Hz), 3.18 (1H, dt, $J$=12.5, 6.1 Hz), 2.45 (3H, s), 2.20-1.50 (7H, s), 1.16 (3H, s), 1.08 (3H, s), 0.85 (9H, s), 0.07 (6H, s); $^{13}$C NMR (100 MHz, CDCl$_3$)δ 144.8, 139.1, 133.6, 132.8, 129.8, 129.2, 127.9, 127.7, 85.3, 84.0, 75.9, 72.9, 71.2, 51.5, 36.3, 29.8, 25.8, 24.9, 24.0, 21.7, 20.7, 18.0, -3.9, -5.1.
[2S,2(2R,5S,5(1R))] 1-iodo-(4-Benzencesulfonyl-2-[5-((1,1-
dimethylethyl)dimethylsilox)-ethyl]-5-methyl-tetrahydro-furan-2-
yl]-butan-2-ol

The mixture of tetrahydrofuranyl ether ix and its diastereomer, (3.5 g, 5.6 mmol) was dissolved in 12 mL of 2-butanone before the addition of sodium iodide (8.4 g, 55.8 mmol) and 18-c-6 (1.5 g, 5.6 mmol). The slurry was heated to a gentle reflux and stirred for 16 h, after which the solution was cooled to room temperature, and 100 mL of saturated brine solution was added. The aqueous phase was separated and extracted with ether (3 x 100 ml), dried over anhydrous Na₂SO₄, and concentrated in vacuo. Purification by flash chromatography (20-50% ethyl acetate/hexanes) gave an inseparable mixture of cis x, and trans iodides (2.6g 80%) as a pale yellow oil.
[2S,2(2R,5S,5(1R))] (4-Benzene-sulfonyl-2-[5-(1-((1,1-dimethylethyl)dimethylsiloxy)-ethyl)-5-methyl-tetrahydro-furan-2-yl]-butan-2-ol

$$\text{Bu}_3\text{SnH, AIBN, toluene} \quad \text{reflux, 6 h}$$

The mixture of iodides were dissolved in 9.2 mL of toluene. First tributyltin hydride (2.5 mL, 9 mmol), and then AIBN (18.5 mg, 0.14 mmol) were added, and the mixture was heated to reflux for 6 h. Direct purification by flash chromatography on silica gel (5%-30% ether/toluene) provided the desired cis isomer xi, (1.2 g, 59%) as a colourless oil.

$^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta$ 7.90-7.50 (5H, m), 3.78 (1H, t, J=7.3 Hz), 3.58 (1H, q, J=6.2 Hz), 3.32 (1H, ddd, J=4.4, 12.5, 16.8 Hz), 3.16 (1H, dt, J=4.8, 12.8 Hz), 2.21 (1H, s), 2.00-1.50 (6, m) 1.09 (3H, s), 1.07 (3H, s), 1.05 (3H, d, J=6.2 Hz), 0.85 (9H, s), 0.05 (3H, s), 0.03 (3H, s); $^{13}\text{C NMR (100 MHz, CDCl}_3\text{)} \delta$ 139.1, 133.6, 129.2, 127.9, 85.0, 84.2, 73.0, 72.1, 51.6, 34.3, 29.6, 25.9, 25.5, 23.8, 20.5, 18.9, 18.0, -4.0, -4.5.
First triethylamine (0.97 mL, 41 mmol) and then trimethylsilyl trifluoromethanesulfonate (0.65 mL, 3.36 mmol) were added to a solution of alcohol xi in 18 mL of dichloromethane at -78°C. After 3h of stirring at -78°C, 1 mL of methanol was added to the reaction mixture. The solution was then warmed to room temperature and 100 mL of saturated brine solution was added. The aqueous phase was separated, extracted with dichloromethane (3 x 200 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (20-40% ethyl acetate/hexanes with 5% triethyl amine) gave fragment xii as a colourless oil (1.3 g, 93%).

¹H NMR (400 MHz, CDCl₃) δ 7.90-7.50 (5H, m), 3.65 (1H, t, J=7.0 Hz), 3.43 (1H, q, J=6.2 Hz) 3.20 (2H, m), 1.95-1.50 (6H, m), 1.06 (3H, s), 1.00 (3H, s), 0.99 (3H, d, J=6.2 Hz), 0.84 (9H, s), 0.02 (3H, s), -0.01 (9H, s); ¹³C NMR (100 MHz, CDCl₃) δ 139.1, 133.4, 129.1, 128.0, 85.7, 82.8, 75.7, 73.4, 52.0, 35.9, 32.7, 26.3, 25.8, 23.0, 18.9, 18.4, 17.9, 2.4, -3.9, -4.8.


